

WHAT IS CLAIMED IS:

1 1. A method of controlling cancer suppression in a mammal having a
2 cancer suppressing gene, comprising the steps of:
3 making a substantially duplicated genetic material corresponding to the
4 genetic material of said gene, the substantially duplicated material selected from the group
5 consisting of a cloned cancer suppressing gene, a modified or defective cancer suppressing
6 gene, homologues thereof, fragments thereof, and mixtures thereof; and
7 interchanging said duplicated genetic material and the cancer suppressing gene
8 of the mammal.

1 2. A method of claim 1, wherein before said making a substantially
2 duplicated genetic material, determining the chromosomal location of said cancer suppressing
3 gene of the mammal.

1 3. A method of claim 1, wherein after said making a substantially
2 duplicated genetic material, detecting the presence or absence of an inactive cancer
3 suppressing gene of a tissue sample of the mammal to determine whether or not the tissue
4 sample cancer suppressing gene is defective or absent.

1 4. A method of claim 3, wherein in response to a determination that the
2 tissue sample cancer suppressing gene is either defective or absent, replacing a cancer
3 suppressing gene of the mammal with its clone.

1 5. A method of claim 3, wherein the determination of whether or not the
2 tissue sample cancer suppressing gene is defective or absent is accomplished by measuring
3 the amount of protein product of said cancer suppressing gene, of the tissue sample, bound by
4 an antibody specific for said protein.

1 6. A method of claim 5, wherein the determination of whether or not the
2 tissue sample cancer suppressing gene is defective or absent is accomplished by:

- 3 (a) labeling said tissue sample with radioactive isotope;
- 4 (b) lysing the labeled tissue;
- 5 (c) reacting the protein product of said cancer suppressing gene with an
- 6 antibody specific for said protein thereby forming a protein/antibody immunocomplex;
- 7 (d) autoradiographing the immunocomplex obtained in step (c); and

8 (e) determining the presence or absence of the protein product by
9 comparing the autoradiogram of step (d) with the autoradiogram of the standard protein
10 product.

1 7. The method of claim 5, wherein the determination of whether or not
2 the tissue sample cancer suppressing gene is defective or absent is accomplished by enzyme
3 immunoassay techniques.

1 8. The method of claim 5, wherein the determination of whether or not
2 the tissue sample cancer suppressing gene is defective or absent is accomplished by
3 immunocytochemistry methods.

1 9. The method of claim 5, wherein the cancer suppressing gene is the RB
2 gene and the protein product is ppRB¹¹⁰.

1 10. The method of claim 1, wherein said cancer suppressing gene is
2 replaced with substantially duplicated material selected from the group consisting of said
3 cloned cancer suppressing gene, homologues thereof, fragments thereof, and mixtures
4 thereof, for therapeutic purposes.

1 11. The method of claim 1, wherein said cancer suppressing gene is
2 replaced with substantially duplicated material selected from the group consisting of said
3 defective cancer suppressing gene, homologues thereof, fragments thereof, and mixtures
4 thereof, for facilitating the testing of the carcinogenicity of environmental influences.

1 12. The method of claim 2, wherein the location of said cancer suppressing
2 gene is determined by chromosome walking.

1 13. The method of claim 2, wherein the location of said cancer suppressing
2 gene is determined through organic markers.

1 14. A method of claim 2, wherein:
2 said chromosomal location of said cancer suppressing gene is determined by
3 testing genes of a chromosome for phenotypic expression;
4 determining one of the genes of said chromosome to be a marker gene; and
5 using chromosomal walking techniques to locate a cancer suppressing gene.

1 15. An animal genetically altered so as to have the allele of at least one
2 cancer suppressing gene selected from the group consisting of a defective allele, a homologue
3 thereof, a fragment thereof, and a mixture thereof.

1 16. An animal of claim 15, wherein said defective allele is selected from
2 the group consisting of defective alleles of RB genes, breast cancer suppressing genes,
3 Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes,
4 bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes,
5 small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes,
6 acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, homologues
7 thereof, fragments thereof, and mixtures thereof.

1 17. An animal of claim 15, wherein said allele contains a DNA fragment
2 having at least one defective nucleotide sequence.

1 18. An animal of claim 15, wherein said defective allele contains a DNA
2 fragment having at least one defective RB nucleotide sequence.

1 19. The animal of claim 15, wherein said animal is a mouse.

1 20. A method for determining the carcinogenicity of suspected
2 environmental influences, using the animal of claim 14, comprising the steps of:
3 exposing said animal to a suspected environmental influence;
4 observing the animal for the phenotypic expression of cancer; and
5 determining carcinogenicity of the suspected environmental influence in
6 response to observing a phenotypic expression of cancer in the animal.

1 21. A method of claim 20, wherein said exposing includes exposing to a
2 source of radiation.

1 22. A method of claim 20, wherein said exposing includes exposing to
2 tobacco combustion products.

1 23. A method of claim 20, wherein said exposing includes exposing to
2 food additives.

1 24. A method of claim 20, wherein said exposing includes exposing to
2 artificial substances.

1 25. A method of claim 20, wherein said observing includes examining the
2 animal for tumor development.

1 26. A method of claim 25, wherein in response to the formation of a tumor
2 in the animal, analyzing the tumor for the presence of cancer cells.

1 27. A method of making the animal of claim 15, comprising:
2 using at least one allele of an animal cancer suppressing gene selected from
3 the group consisting of a defective allele, a homologue thereof, a fragment thereof, and a
4 mixture thereof;

5 mutating at least one animal cell with said allele to form a mutated cell;
6 introducing said mutated cell into an animal blastocyst;
7 permitting growth of the blastocyst for a given period of time sufficient to
8 incorporate said allele into its cells; repressing genetic recombinations within said cells;
9 transferring the blastocyst containing said allele into the uterus of a pseudo pregnant animal
10 for giving birth subsequently to an animal bearing said allele;

11 breeding said animal to reproduce additional animals; and
12 selecting the animal of claim 14 from said additional animals by determining
13 the presence therein of the said allele.

1 28. A method of claim 27, wherein before introducing said allele,
2 removing said blastocyst from a super ovulated animal, and wherein said blastocyst is
3 comprised of undifferentiated cells.

1 29. A method of claim 27, wherein said introducing is performed in vitro.

1 30. A pharmaceutical composition wherein the active ingredient is selected
2 from the group consisting of a naturally occurring intact cancer suppressing gene, a cloned
3 intact cancer suppressing gene, fragments thereof, homolgues thereof and mixtures thereof.

1 31. A pharmaceutical composition of claim 30, wherein said naturally
2 occurring and cloned cancer suppressing gene is selected from the group consisting of RB
3 genes, breast cancer suppressing genes, Wilm's tumor suppressing genes, Beckwith-

4 Wiedemann syndrome suppressing genes, bladder transitional cell carcinoma suppressing
5 genes, neuroblastoma suppressing genes, small cell lung carcinoma suppressing genes, renal
6 cell carcinoma suppressing genes, acoustic neuroma suppressing genes, colorectal carcinoma
7 suppressing genes, homologues thereof, fragments thereof, and mixtures thereof.

1 32. A pharmaceutical composition of claim 30, wherein the active
2 ingredient is selected from the group consisting of RB cDNA, modified RB cDNA fragment,
3 clones thereof, homologues thereof and mixtures thereof.

1 33. A pharmaceutical composition of claim 31, wherein the active
2 ingredient for each of said gene is selected from the group consisting of cDNA of said gene,
3 fragments of said cDNA, homologues thereof and mixtures thereof.

1 34. A pharmaceutical composition of claim 32, wherein the cancer
2 suppressing gene is isolated from human chromosome 13 region 13q14.

1 35. A pharmaceutical composition of claim 31, wherein the cancer
2 suppressing gene and its clone each has the following nucleotide sequence:

3
4
5 TTCCGGTTTT TCTCAGGGGA CGTTGAAATT ATTTTGTAA CGGGAGTCGG GAGAGGACGG 60
6
7 GGCGTGCCCC GCGTGCGCGC GCGTCGTCCT CCGGGCGCT CCTCCACAGC TCGCTGGCTC 120
8
9 CCGCCGCGGA AAGGCGTC ATG CCG CCC AAA ACC CCC CGA AAA ACG GCC GCC 171
10 Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala
11 1 5 10
12
13 ACC GCC GCC GCT GCC GCC GCG GAA CCC CCG GCA CCG CCG CCG CCG CCC 219
14 Thr Ala Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro Pro
15 15 20 25
16
17 CCT CCG TAG GAG GAC CCA GAG CAG GAC AGC GGC CCG GAG GAC CTG CCT 267
18 Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro
19 30 35 40
20
21 CTC GTC AGG CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA 315
22 Leu Val Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala
23 45 50 55
24
25 TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG 363
26 Leu Cys Gln Lys Leu Lys Ile Pro Asp His Val Arg Glu Arg Ala Trp
27 60 65 70 75
28
29 TTA ACT TGG GAG AAA GTT TCA TCT GTG GAT GGA GTA TTG GGA GGT TAT 411
30 Leu Thr Trp Glu Lys Val Ser Ser Val Asp Gly Val Leu Gly Gly Tyr
31 80 85 90
32

33	ATT	CAA	AAG	AAA	AAG	GAA	CTG	TGG	GGA	ATC	TGT	ATC	TTT	ATT	GCA	GCA	459
34	Ile	Gln	Lys	Lys	Lys	Glu	Leu	Trp	Gly	Ile	Cys	Ile	Phe	Ile	Ala	Ala	
35				95					100						105		
36																	
37	GTT	GAC	CTA	GAT	GAG	ATG	TCG	TTC	ACT	TTT	ACT	GAG	CTA	CAG	AAA	AAC	507
38	Val	Asp	Leu	Asp	Glu	Met	Ser	Phe	Thr	Phe	Thr	Glu	Leu	Gln	Lys	Asn	
39			110					115					120				
40																	
41	ATA	GAA	ATC	AGT	GTC	CAT	AAA	TTC	TTT	AAC	TTA	CTA	AAA	GAA	ATT	GAT	555
42	Ile	Glu	Ile	Ser	Val	His	Lys	Phe	Phe	Asn	Leu	Leu	Lys	Glu	Ile	Asp	
43		125					130					135					
44																	
45	ACC	AGT	ACC	AAA	GTT	GAT	AAT	GCT	ATG	TCA	AGA	CTG	TTG	AAG	AAG	TAT	603
46	Thr	Ser	Thr	Lys	Val	Asp	Asn	Ala	Met	Ser	Arg	Leu	Leu	Lys	Lys	Tyr	
47	140					145					150					155	
48																	
49	GAT	GTA	TTG	TTT	GCA	CTC	TTC	AGC	AAA	TTG	GAA	AGG	ACA	TGT	GAA	CTT	651
50	Asp	Val	Leu	Phe	Ala	Leu	Phe	Ser	Lys	Leu	Glu	Arg	Thr	Cys	Glu	Leu	
51					160					165					170		
52																	
53	ATA	TAT	TTG	ACA	CAA	CCC	AGC	AGT	TCG	ATA	TCT	ACT	GAA	ATA	AAT	TCT	699
54	Ile	Tyr	Leu	Thr	Gln	Pro	Ser	Ser	Ser	Ile	Ser	Thr	Glu	Ile	Asn	Ser	
55				175					180						185		
56																	
57	GCA	TTG	GTG	CTA	AAA	GTT	TCT	TGG	ATC	ACA	TTT	TTA	TTA	GCT	AAA	GGG	747
58	Ala	Leu	Val	Leu	Lys	Val	Ser	Trp	Ile	Thr	Phe	Leu	Leu	Ala	Lys	Gly	
59			190					195					200				
60																	
61	GAA	GTA	TTA	CAA	ATG	GAA	GAT	GAT	CTG	GTG	ATT	TCA	TTT	CAG	TTA	ATG	795
62	Glu	Val	Leu	Gln	Met	Glu	Asp	Asp	Leu	Val	Ile	Ser	Phe	Gln	Leu	Met	
63		205					210					215					
64	CTA	TGT	GTC	CTT	GAC	TAT	TTT	ATT	AAA	CTC	TCA	CCT	CCC	ATG	TTG	CTC	843
65	Leu	Cys	Val	Leu	Asp	Tyr	Phe	Ile	Lys	Leu	Ser	Pro	Pro	Met	Leu	Leu	
66	220				225						230					235	
67																	
68	AAA	GAA	CCA	TAT	AAA	ACA	GCT	GTT	ATA	CCC	ATT	AAT	GGT	TCA	CCT	CGA	891
69	Lys	Glu	Pro	Tyr	Lys	Thr	Ala	Val	Ile	Pro	Ile	Asn	Gly	Ser	Pro	Arg	
70					240					245					250		
71																	
72	ACA	CCC	AGG	CGA	GGT	CAG	AAC	AGG	AGT	GCA	CGG	ATA	GCA	AAA	CAA	CTA	939
73	Thr	Pro	Arg	Arg	Gly	Gln	Asn	Arg	Ser	Ala	Arg	Ile	Ala	Lys	Gln	Leu	
74				255					260					265			
75																	
76	GAA	AAT	GAT	ACA	AGA	ATT	ATT	GAA	GTT	CTC	TGT	AAA	GAA	CAT	GAA	TGT	987
77	Glu	Asn	Asp	Thr	Arg	Ile	Ile	Glu	Val	Leu	Cys	Lys	Glu	His	Glu	Cys	
78			270					275					280				
79																	
80	AAT	ATA	GAT	GAG	GTG	AAA	AAT	GTT	TAT	TTC	AAA	AAT	TTT	ATA	CCT	TTT	1035
81	Asn	Ile	Asp	Glu	Val	Lys	Asn	Val	Tyr	Phe	Lys	Asn	Phe	Ile	Pro	Phe	
82		285					290					295					
83																	
84	ATG	AAT	TCT	CTT	GGA	CTT	GTA	ACA	TCT	AAT	GGA	CTT	CCA	GAG	GTT	GAA	1083
85	Met	Asn	Ser	Leu	Gly	Leu	Val	Thr	Ser	Asn	Gly	Leu	Pro	Glu	Val	Glu	
86	300				305						310					315	
87																	
88	AAT	CTT	TCT	AAA	CGA	TAC	GAA	GAA	ATT	TAT	CTT	AAA	AAT	AAA	GAT	CTA	1131
89	Asn	Leu	Ser	Lys	Arg	Tyr	Glu	Glu	Ile	Tyr	Leu	Lys	Asn	Lys	Asp	Leu	
90					320					325					330		
91																	
92	GAT	GCA	AGA	TTA	TTT	TTG	GAT	CAT	GAT	AAA	ACT	CTT	CAG	ACT	GAT	TCT	1179
93	Asp	Ala	Arg	Leu	Phe	Leu	Asp	His	Asp	Lys	Thr	Leu	Gln	Thr	Asp	Ser	

94				335				340					345				
95																	
96	ATA	GAC	AGT	TTT	GAA	ACA	CAG	AGA	ACA	CCA	CGA	AAA	AGT	AAC	CTT	GAT	1227
97	Ile	Asp	Ser	Phe	Glu	Thr	Gln	Arg	Thr	Pro	Arg	Lys	Ser	Asn	Leu	Asp	
98				350				355					360				
99																	
100	GAA	GAG	GTG	AAT	GTA	ATT	CCT	CCA	CAC	ACT	CCA	GTT	AGG	ACT	GTT	ATG	1275
101	Glu	Glu	Val	Asn	Val	Ile	Pro	Pro	His	Thr	Pro	Val	Arg	Thr	Val	Met	
102				365				370					375				
103																	
104	AAC	ACT	ATC	CAA	CAA	TTA	ATG	ATG	ATT	TTA	AAT	TCA	GCA	AGT	GAT	CAA	1323
105	Asn	Thr	Ile	Gln	Gln	Leu	Met	Met	Ile	Leu	Asn	Ser	Ala	Ser	Asp	Gln	
106	380					385					390					395	
107																	
108	CCT	TCA	GAA	AAT	CTG	ATT	TCC	TAT	TTT	AAC	AAC	TGC	ACA	GTG	AAT	CCA	1371
109	Pro	Ser	Glu	Asn	Leu	Ile	Ser	Tyr	Phe	Asn	Asn	Cys	Thr	Val	Asn	Pro	
110					400					405					410		
111																	
112	AAA	GAA	AGT	ATA	CTG	AAA	AGA	GTG	AAG	GAT	ATA	GGA	TAC	ATC	TTT	AAA	1419
113	Lys	Glu	Ser	Ile	Leu	Lys	Arg	Val	Lys	Asp	Ile	Gly	Tyr	Ile	Phe	Lys	
114				415					420					425			
115																	
116	GAG	AAA	TTT	GCT	AAA	GCT	GTG	GGA	CAG	GGT	TGT	GTC	GAA	ATT	GGA	TCA	1467
117	Glu	Lys	Phe	Ala	Lys	Ala	Val	Gly	Gln	Gly	Cys	Val	Glu	Ile	Gly	Ser	
118				430				435					440				
119																	
120	CAG	CGA	TAC	AAA	CTT	GGA	GTT	CGC	TTG	TAT	TAC	CGA	GTA	ATG	GAA	TCC	1515
121	Gln	Arg	Tyr	Lys	Leu	Gly	Val	Arg	Leu	Tyr	Tyr	Arg	Val	Met	Glu	Ser	
122		445					450					455					
123																	
124	ATG	CTT	AAA	TCA	GAA	GAA	GAA	CGA	TTA	TCC	ATT	CAA	AAT	TTT	AGC	AAA	1563
125	Met	Leu	Lys	Ser	Glu	Glu	Glu	Arg	Leu	Ser	Ile	Gln	Asn	Phe	Ser	Lys	
126	460					465					470					475	
127																	
128	CTT	CTG	AAT	GAC	AAC	ATT	TTT	CAT	ATG	TCT	TTA	TTG	GCG	TGC	GCT	CTT	1611
129	Leu	Leu	Asn	Asp	Asn	Ile	Phe	His	Met	Ser	Leu	Leu	Ala	Cys	Ala	Leu	
130					480					485					490		
131																	
132	GAG	GTT	GTA	ATG	GCC	ACA	TAT	AGC	AGA	AGT	ACA	TCT	CAG	AAT	CTT	GAT	1659
133	Glu	Val	Val	Met	Ala	Thr	Tyr	Ser	Arg	Ser	Thr	Ser	Gln	Asn	Leu	Asp	
134				495					500					505			
135																	
136	TCT	GGA	ACA	GAT	TTG	TCT	TTC	CCA	TGG	ATT	CTG	AAT	GTG	CTT	AAT	TTA	1707
137	Ser	Gly	Thr	Asp	Leu	Ser	Phe	Pro	Trp	Ile	Leu	Asn	Val	Leu	Asn	Leu	
138				510				515					520				
139																	
140	AAA	GCC	TTT	GAT	TTT	TAC	AAA	GTG	ATC	GAA	AGT	TTT	ATC	AAA	GCA	GAA	1755
141	Lys	Ala	Phe	Asp	Phe	Tyr	Lys	Val	Ile	Glu	Ser	Phe	Ile	Lys	Ala	Glu	
142		525					530					535					
143																	
144	GGC	AAC	TTG	ACA	AGA	GAA	ATG	ATA	AAA	CAT	TTA	GAA	CGA	TGT	GAA	CAT	1803
145	Gly	Asn	Leu	Thr	Arg	Glu	Met	Ile	Lys	His	Leu	Glu	Arg	Cys	Glu	His	
146	540					545					550					555	
147																	
148	CGA	ATC	ATG	GAA	TCC	CTT	GCA	TGG	CTC	TCA	GAT	TCA	CCT	TTA	TTT	GAT	1851
149	Arg	Ile	Met	Glu	Ser	Leu	Ala	Trp	Leu	Ser	Asp	Ser	Pro	Leu	Phe	Asp	
150					560					565					570		
151																	
152	CTT	ATT	AAA	CAA	TCA	AAG	GAC	CGA	GAA	GGA	CCA	ACT	GAT	CAC	CTT	GAA	1899
153	Leu	Ile	Lys	Gln	Ser	Lys	Asp	Arg	Glu	Gly	Pro	Thr	Asp	His	Leu	Glu	
154				575				580						585			

62

216	AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG	2667
217	Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu	
218	830 835 840	
219		
220	AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC	2715
221	Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu	
222	845 850 855	
223		
224	AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA	2763
225	Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu	
226	860 865 870 875	
227		
228	CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC	2811
229	Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu	
230	880 885 890	
231		
232	CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT	2859
233	Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr	
234	895 900 905	
235		
236	CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA	2907
237	Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser	
238	910 915 920	
239		
240	AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT	2962
241	Asn Lys Glu Glu Lys	
242	925	
243		
244	GGATTCATTG TCTCTCACAG ATGTGACTGT AT	2994

1 36. A pharmaceutical composition of claim 32, wherein said RB cDNA
2 fragment is selected from the group consisting of RB-1, RB-2, RB-5, y79R8 and mixtures
3 thereof.

1 37. A pharmaceutical composition of claim 32, wherein a resulting mRNA
2 transcript of said RB cDNA fragment has 4.6 kb.

1 38. A pharmaceutical composition of claim 37, wherein the cloned
2 genomic DNA has at least 27 exons.

1 39. A pharmaceutical composition of claim 30, wherein the cloned RB
2 cDNA transcribes into mRNA which translates in protein having an amino acid sequence
3 comprising:

4 [M]PPKTPRKTAATAAAAAAAEPPAPPPPPPPPEEDPE (34)
 5 QDSGPEDLPLVRLEFEETEEDFTALCQKLKIPDHVRERA (74)
 6 WLTWEKVSSVDGVLGGYIQKKKELWGICIFIAAVDLDEM[S] (114)
 7 FTFTELQKNIEISVHKFFNLLKEIDTSTKVDNAMSRLKK (154)
 8 YDVLFAFASKLERTCELIYLTQPSSSISTEINSALVLKVS (194)
 9 WITFLLAKGEVLQMEDDLVISFQLNLCVLDYFIKLSPPML (234)
 10 LKEPYKTAVIPINGSRTPRRGQMRSARIAKQLENDTRII (274)
 11 EVLCKEHECNIDEVKNVYFKNFIPFMNSLGLVTSNGLPEV (314)
 12 ENLSKRYEEIYLKNKDLDDLARLFLDHDKTLQTDSDSIDSFETQ (354)
 13 RTPRKSNDDEEVNVIPTHTPVRTVMNTIQQLMMILNSASD (394)
 14 QPSENLI SYFNNCTVNPKE SILKRVKDIGYIFKEKFAKAV (434)
 15 GQGCVEIGSQRYKLGVRLYYRVMESMLKSEEERLSIQNFS (474)
 16 KLLNDNIFHMSLLACALEVVMATYSRSTSQNLDSTGTDLSF (514)
 17 PWILNVLNLKAFDFYKVIESFIKAEGNLTREMIKHLERCE (554)
 18 HRIMESLAWLSDSPLFDLIKQSKDREGPTDHLESACPLNL (594)
 19 PLQNNHTAADMYLSPVRSPPKKKGSTTRVNSTANAETQATS (634)
 20 AFQTQKPLKSTSLSLFYKKVYRLAYLRLNTLCERLLSEHP (674)
 21 ELEHIIWTLFQHTLQNEYELMRDRHLDQIMMCSMYGICKV (714)
 22 KNIDLKFKIIVTAYKDLPHAVQETFKRVLIKEEEYDSIIV (754)
 23 FYNSVFMQRLKTNILQYASTRPPTLSPIPHIPRSPYKFPS (794)
 24 SPLRIPGGNIYISPLKSPYKISEGLPTPTKMTPRSRILVS (834)
 25 IGESFGTSEKFQKINQMVCSNDRVLKRS AEGSNPPKPLKK (874)
 26 LRFDIEGSDEADGSKHLPGESKFQQLAEMTSTRTRMQKQ (914)
 27 KMND SMDTSNKEEK (928)
 28
 29

30 single-letter abbreviations for the amino acid residues are:
 31 A, Ala; C, Cys; D, Asp; E, Gly; F, Phe; G, Gly; H, His;
 32 I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln;
 33 R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

1 40. A DNA nucleotide sequence comprising:
 2
 3 TTCCGGTTTT TCTCAGGGGA CGTTGAAATT ATTTTGTAA CGGGAGTCGG GAGAGGACGG 60
 4
 5 GGCGTGCCCC GCGTGCGCGC GCGTCGTCCT CCCC GGCGCT CCTCCACAGC TCGCTGGCTC 120
 6
 7 CCGCCGCGGA AAGGCGTC ATG CCG CCC AAA ACC CCC CGA AAA ACG GCC GCC 171
 8 Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala
 9 1 5 10
 10
 11 ACC GCC GCC GCT GCC GCC GCG GAA CCC CCG GCA CCG CCG CCG CCG CCC 219
 12 Thr Ala Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro Pro
 13 15 20 25
 14
 15 CCT CCG TAG GAG GAC CCA GAG CAG GAC AGC GGC CCG GAG GAC CTG CCT 267
 16 Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro
 17 30 35 40
 18
 19 CTC GTC AGG CTT GAG TTT GAA GAA ACA GAA GAA CCT GAT TTT ACT GCA 315
 20 Leu Val Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala
 21 45 50 55
 22
 23 TTA TGT CAG AAA TTA AAG ATA CCA GAT CAT GTC AGA GAG AGA GCT TGG 363

24	Leu	Cys	Gln	Lys	Leu	Lys	Ile	Pro	Asp	His	Val	Arg	Glu	Arg	Ala	Trp	
25	60					65					70					75	
26																	
27	TTA	ACT	TGG	GAG	AAA	GTT	TCA	TCT	GTG	GAT	GGA	GTA	TTG	GGA	GGT	TAT	411
28	Leu	Thr	Trp	Glu	Lys	Val	Ser	Ser	Val	Asp	Gly	Val	Leu	Gly	Gly	Tyr	
29					80					85					90		
30																	
31	ATT	CAA	AAG	AAA	AAG	GAA	CTG	TGG	GGA	ATC	TGT	ATC	TTT	ATT	GCA	GCA	459
32	Ile	Gln	Lys	Lys	Lys	Glu	Leu	Trp	Gly	Ile	Cys	Ile	Phe	Ile	Ala	Ala	
33				95					100					105			
34																	
35	GTT	GAC	CTA	GAT	GAG	ATG	TCG	TTC	ACT	TTT	ACT	GAG	CTA	CAG	AAA	AAC	507
36	Val	Asp	Leu	Asp	Glu	Met	Ser	Phe	Thr	Phe	Thr	Glu	Leu	Gln	Lys	Asn	
37			110					115					120				
38																	
39	ATA	GAA	ATC	AGT	GTC	CAT	AAA	TTC	TTT	AAC	TTA	CTA	AAA	GAA	ATT	GAT	555
40	Ile	Glu	Ile	Ser	Val	His	Lys	Phe	Phe	Asn	Leu	Leu	Lys	Glu	Ile	Asp	
41		125					130					135					
42																	
43	ACC	AGT	ACC	AAA	GTT	GAT	AAT	GCT	ATG	TCA	AGA	CTG	TTG	AAG	AAG	TAT	603
44	Thr	Ser	Thr	Lys	Val	Asp	Asn	Ala	Met	Ser	Arg	Leu	Leu	Lys	Lys	Tyr	
45	140					145					150					155	
46																	
47	GAT	GTA	TTG	TTT	GCA	CTC	TTC	AGC	AAA	TTG	GAA	AGG	ACA	TGT	GAA	CTT	651
48	Asp	Val	Leu	Phe	Ala	Leu	Phe	Ser	Lys	Leu	Glu	Arg	Thr	Cys	Glu	Leu	
49					160					165					170		
50																	
51	ATA	TAT	TTG	ACA	CAA	CCC	AGC	AGT	TCG	ATA	TCT	ACT	GAA	ATA	AAT	TCT	699
52	Ile	Tyr	Leu	Thr	Gln	Pro	Ser	Ser	Ser	Ile	Ser	Thr	Glu	Ile	Asn	Ser	
53				175					180					185			
54																	
55	GCA	TTG	GTG	CTA	AAA	GTT	TCT	TGG	ATC	ACA	TTT	TTA	TTA	GCT	AAA	GGG	747
56	Ala	Leu	Val	Leu	Lys	Val	Ser	Trp	Ile	Thr	Phe	Leu	Leu	Ala	Lys	Gly	
57			190					195					200				
58																	
59	GAA	GTA	TTA	CAA	ATG	GAA	GAT	GAT	CTG	GTG	ATT	TCA	TTT	CAG	TTA	ATG	795
60	Glu	Val	Leu	Gln	Met	Glu	Asp	Asp	Leu	Val	Ile	Ser	Phe	Gln	Leu	Met	
61		205					210					215					
62	CTA	TGT	GTC	CTT	GAC	TAT	TTT	ATT	AAA	CTC	TCA	CCT	CCC	ATG	TTG	CTC	843
63	Leu	Cys	Val	Leu	Asp	Tyr	Phe	Ile	Lys	Leu	Ser	Pro	Pro	Met	Leu	Leu	
64	220					225				230						235	
65																	
66	AAA	GAA	CCA	TAT	AAA	ACA	GCT	GTT	ATA	CCC	ATT	AAT	GGT	TCA	CCT	CGA	891
67	Lys	Glu	Pro	Tyr	Lys	Thr	Ala	Val	Ile	Pro	Ile	Asn	Gly	Ser	Pro	Arg	
68					240					245					250		
69																	
70	ACA	CCC	AGG	CGA	GGT	CAG	AAC	AGG	AGT	GCA	CGG	ATA	GCA	AAA	CAA	CTA	939
71	Thr	Pro	Arg	Arg	Gly	Gln	Asn	Arg	Ser	Ala	Arg	Ile	Ala	Lys	Gln	Leu	
72				255					260					265			
73																	
74	GAA	AAT	GAT	ACA	AGA	ATT	ATT	GAA	GTT	CTC	TGT	AAA	GAA	CAT	GAA	TGT	987
75	Glu	Asn	Asp	Thr	Arg	Ile	Ile	Glu	Val	Leu	Cys	Lys	Glu	His	Glu	Cys	
76			270					275					280				
77																	
78	AAT	ATA	GAT	GAG	GTG	AAA	AAT	GTT	TAT	TTC	AAA	AAT	TTT	ATA	CCT	TTT	1035
79	Asn	Ile	Asp	Glu	Val	Lys	Asn	Val	Tyr	Phe	Lys	Asn	Phe	Ile	Pro	Phe	
80		285					290					295					
81																	
82	ATG	AAT	TCT	CTT	GGA	CTT	GTA	ACA	TCT	AAT	GGA	CTT	CCA	GAG	GTT	GAA	1083
83	Met	Asn	Ser	Leu	Gly	Leu	Val	Thr	Ser	Asn	Gly	Leu	Pro	Glu	Val	Glu	
84	300					305					310					315	

85																	
86	AAT	CTT	TCT	AAA	CGA	TAC	GAA	GAA	ATT	TAT	CTT	AAA	AAT	AAA	GAT	CTA	1131
87	Asn	Leu	Ser	Lys	Arg	Tyr	Glu	Glu	Ile	Tyr	Leu	Lys	Asn	Lys	Asp	Leu	
88					320					325					330		
89																	
90	GAT	GCA	AGA	TTA	TTT	TTG	GAT	CAT	GAT	AAA	ACT	CTT	CAG	ACT	GAT	TCT	1179
91	Asp	Ala	Arg	Leu	Phe	Leu	Asp	His	Asp	Lys	Thr	Leu	Gln	Thr	Asp	Ser	
92				335					340					345			
93																	
94	ATA	GAC	AGT	TTT	GAA	ACA	CAG	AGA	ACA	CCA	CGA	AAA	AGT	AAC	CTT	GAT	1227
95	Ile	Asp	Ser	Phe	Glu	Thr	Gln	Arg	Thr	Pro	Arg	Lys	Ser	Asn	Leu	Asp	
96			350					355					360				
97																	
98	GAA	GAG	GTG	AAT	GTA	ATT	CCT	CCA	CAC	ACT	CCA	GTT	AGG	ACT	GTT	ATG	1275
99	Glu	Glu	Val	Asn	Val	Ile	Pro	Pro	His	Thr	Pro	Val	Arg	Thr	Val	Met	
100		365					370					375					
101																	
102	AAC	ACT	ATC	CAA	CAA	TTA	ATG	ATG	ATT	TTA	AAT	TCA	GCA	AGT	GAT	CAA	1323
103	Asn	Thr	Ile	Gln	Gln	Leu	Met	Met	Ile	Leu	Asn	Ser	Ala	Ser	Asp	Gln	
104	380					385				390						395	
105																	
106	CCT	TCA	GAA	AAT	CTG	ATT	TCC	TAT	TTT	AAC	AAC	TGC	ACA	GTG	AAT	CCA	1371
107	Pro	Ser	Glu	Asn	Leu	Ile	Ser	Tyr	Phe	Asn	Asn	Cys	Thr	Val	Asn	Pro	
108					400					405					410		
109																	
110	AAA	GAA	AGT	ATA	CTG	AAA	AGA	GTG	AAG	GAT	ATA	GGA	TAC	ATC	TTT	AAA	1419
111	Lys	Glu	Ser	Ile	Leu	Lys	Arg	Val	Lys	Asp	Ile	Gly	Tyr	Ile	Phe	Lys	
112				415					420					425			
113																	
114	GAG	AAA	TTT	GCT	AAA	GCT	GTG	GGA	CAG	GGT	TGT	GTC	GAA	ATT	GGA	TCA	1467
115	Glu	Lys	Phe	Ala	Lys	Ala	Val	Gly	Gln	Gly	Cys	Val	Glu	Ile	Gly	Ser	
116			430					435				440					
117																	
118	CAG	CGA	TAC	AAA	CTT	GGA	GTT	CGC	TTG	TAT	TAC	CGA	GTA	ATG	GAA	TCC	1515
119	Gln	Arg	Tyr	Lys	Leu	Gly	Val	Arg	Leu	Tyr	Tyr	Arg	Val	Met	Glu	Ser	
120		445					450					455					
121																	
122	ATG	CTT	AAA	TCA	GAA	GAA	GAA	CGA	TTA	TCC	ATT	CAA	AAT	TTT	AGC	AAA	1563
123	Met	Leu	Lys	Ser	Glu	Glu	Glu	Arg	Leu	Ser	Ile	Gln	Asn	Phe	Ser	Lys	
124	460					465				470						475	
125																	
126	CTT	CTG	AAT	GAC	AAC	ATT	TTT	CAT	ATG	TCT	TTA	TTG	GCG	TGC	GCT	CTT	1611
127	Leu	Leu	Asn	Asp	Asn	Ile	Phe	His	Met	Ser	Leu	Leu	Ala	Cys	Ala	Leu	
128					480					485					490		
129																	
130	GAG	GTT	GTA	ATG	GCC	ACA	TAT	AGC	AGA	AGT	ACA	TCT	CAG	AAT	CTT	GAT	1659
131	Glu	Val	Val	Met	Ala	Thr	Tyr	Ser	Arg	Ser	Thr	Ser	Gln	Asn	Leu	Asp	
132				495					500					505			
133																	
134	TCT	GGA	ACA	GAT	TTG	TCT	TTC	CCA	TGG	ATT	CTG	AAT	GTG	CTT	AAT	TTA	1707
135	Ser	Gly	Thr	Asp	Leu	Ser	Phe	Pro	Trp	Ile	Leu	Asn	Val	Leu	Asn	Leu	
136			510					515					520				
137																	
138	AAA	GCC	TTT	GAT	TTT	TAC	AAA	GTG	ATC	GAA	AGT	TTT	ATC	AAA	GCA	GAA	1755
139	Lys	Ala	Phe	Asp	Phe	Tyr	Lys	Val	Ile	Glu	Ser	Phe	Ile	Lys	Ala	Glu	
140		525					530					535					
141																	
142	GGC	AAC	TTG	ACA	AGA	GAA	ATG	ATA	AAA	CAT	TTA	GAA	CGA	TGT	GAA	CAT	1803
143	Gly	Asn	Leu	Thr	Arg	Glu	Met	Ile	Lys	His	Leu	Glu	Arg	Cys	Glu	His	
144	540					545					550					555	
145																	

207 Pro Leu Arg Ile Pro Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser
208 800 805 810
209
210 CCA TAT AAA ATT TCA GAA GGT CTG CCA ACA CCA ACA AAA ATG ACT CCA 2619
211 Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro
212 815 820 825
213
214 AGA TCA AGA ATC TTA GTA TCA ATT GGT GAA TCA TTC GGG ACT TCT GAG 2667
215 Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu
216 830 835 840
217
218 AAG TTC CAG AAA ATA AAT CAG ATG GTA TGT AAC AGC GAC CGT GTG CTC 2715
219 Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu
220 845 850 855
221
222 AAA AGA AGT GCT GAA GGA AGC AAC CCT CCT AAA CCA CTG AAA AAA CTA 2763
223 Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu
224 860 865 870 875
225
226 CGC TTT GAT ATT GAA GGA TCA GAT GAA GCA GAT GGA AGT AAA CAT CTC 2811
227 Arg Phe Asp Ile Glu Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu
228 880 885 890
229
230 CCA GGA GAG TCC AAA TTT CAG CAG AAA CTG GCA GAA ATG ACT TCT ACT 2859
231 Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr
232 895 900 905
233
234 CGA ACA CGA ATG CAA AAG CAG AAA ATG AAT GAT AGC ATG GAT ACC TCA 2907
235 Arg Thr Arg Met Gln Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser
236 910 915 920
237
238 AAC AAG GAA GAG AAA TGAGGATCTC AGGACCTTGG TGGACACTGT GTACACCTCT 2962
239 Asn Lys Glu Glu Lys
240 925
241
242 GGATTCATTG TCTCTCACAG ATGTGACTGT AT 2994

1 41. A method of therapeutically treating inactive, mutative or absent
2 cancer suppressing genes comprising:
3 treating said inactive, mutative or absent cancer suppressing genes with at
4 least a portion of intact cancer suppressing genes.

1 42. A method of claim 41, wherein said cancer suppressing genes are each
2 a substance selected from the groups consisting of RB genes, breast cancer suppressing
3 genes, Wilm's tumor suppressing genes, Beckwith-Wiedemann syndrome suppressing genes,
4 bladder transitional cell carcinoma suppressing genes, neuroblastoma suppressing genes,
5 small cell lung carcinoma suppressing genes, renal cell carcinoma suppressing genes,
6 acoustic neuroma suppressing genes, colorectal carcinoma suppressing genes, and mixtures
7 thereof.

1 43. A method of claim 41, wherein said treating includes:

2 treating said inactive, mutative or absent cancer suppressing gene with a
3 substance selected from the group consisting of an RB gene, a portion of said gene, or a
4 mixture thereof.

1 44. A method of claim 43, wherein said portion is selected from the group
2 consisting of RB cDNA, RB cDNA fragment, homologues thereof and mixtures thereof.

1 45. The method of claim 41, wherein the intact cancer suppressing gene, or
2 portion thereof, is delivered to the site of a tumor by means of a retrovirus.

1 46. A method of claim 41, wherein the intact cancer suppressing gene, or a
2 portion thereof, is delivered to the site of a tumor by a liposome.

1 47. A method of claim 41, wherein the location of said cancer suppressing
2 gene is determined by utilizing a genetic marker.